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cont.

[the] ITR sequences,
an encapsulation sequence,
a heterologous DNA sequence, and
all or part of an E4 gene,

wherein the E4 gene or part thereof is the sole adenoviral gene.

REMARKS

Status of the Claims

Claims 1-3, 6, and 9-35 are under consideration. Claims 1, 2-3, 6, 9, 10, 12-16, 10-22, 24-27, 32, and 33 have been amended to correct matters of form. The amendments do not affect the scope of the claimed subject matter. Support for the amendment of claim 13 is found in the specification at page 7, line 5 (proteins), lines 28-29 (list of well known neurotrophic factors), and lines 33-34 (coagulation factors, including examples of well known coagulation factors). The amendments of claims 34 and 35 are supported in the specification at page 18, lines 24-25 and Figure 4, and page 20, lines 7-8 and Figure 5. All of the claims under consideration, as amended, are presented as an Appendix attached hereto.

Summary of the Office Action

Applicants acknowledge with appreciation the Examiner's statement that claims 1, 11, 19, 31, and 33 are considered allowable. Office Action at page 4.

Claims 2-3, 6, 9, 10, 12-18, 20-30, 32, 34, and 35 stand rejected under 35 U.S.C. § 112, second paragraph. Claims 34 and 35 stand rejected under 35 U.S.C. § 102(b) over Berkner et al., 1988, BioTechniques 6:616 (hereinafter "Berkner") or Bajocchi et al., 1993, Nature Genetics 3:229 (hereinafter "Bajocchi").

For the reasons set forth below, Applicants submit that all of the claims satisfy the criteria for patentability, particularly under 35 U.S.C. §§ 112 and 102, and are in condition for allowance.

Discussion of Rejections Under 35 U.S.C. § 112

The Examiner contends that claims 2-3, 6, 9, 10, 12-18, 20-30, and 32 are vague and indefinite because of the phrase "characterized in that" and has suggested substitution of the term "wherein" in its place.

Applicants appreciate the Examiner's helpful suggestion and have amended claims 2-3, 6, 9, 10, 12-16, 20-22, and 24-27 to insert the term "wherein" in place of "characterized in that" to place these claims in condition for allowance. Applicants note that claims 17, 18, 23, 28, and 30 already lack the objected to recitation "characterized in that". Claims 17 and 18 were amended to replace "characterized in that" with "wherein" in the amendment filed May 6, 1996, while claims 23, 28, and 30 never recited the term. None of these claims have been rejected on any other grounds.

In view of the foregoing amendments and remarks, Applicants submit that the rejection should be withdrawn and claims 2-3, 6, 9, 10, 12, 14-18, 20-30 and 32 are in condition for allowance.

The Examiner contends that the elements of the Markush group of claim 13 are vague and indefinite. The Examiner contends that neurotransmitters and precursors of neurotransmitters are chemical compounds and not gene products; and that the terms "blood derivatives", "synthetic enzymes", "trophic factors", and "genes encoding factors involved in coagulation" are unclear.

Applicants have amended claim 13 to delete the terms neurotransmitters and precursors of neurotransmitters, to correct "blood derivatives" to "blood proteins", to delete the term "synthetic enzymes", to recite "neurotrophic factors" instead of "trophic factors", and to recite "coagulation factors." Applicants submit that blood proteins, neurotrophic factors, and coagulation factors are all well known therapeutic gene products clearly intended by the claims in view of the specification (see the specification, *e.g.*, at page 7, lines 5-34).

In view of the foregoing amendments and remarks, Applicants submit that this basis for the rejection of claim 13 is obviated, should be withdrawn, and that claim 13 is in condition for allowance.

The Examiner contends that claim 33 is vague and indefinite in the use of the term "ORF 6/7," further alleging that this is not an art recognized term.

Applicants respectfully disagree. "ORF" is the well known abbreviation for "open reading frame." Open reading frames (ORF) 6 and 6/7 are found in the E4 region of adenovirus, as set forth in the specification at page 25, lines 29-30. Cell lines modified to express these open reading frames are described in Example 4 (page 20, line 18 to page 21, line 34), as noted on page 25, lines 33-34. Applicants further submit that the term "ORF" (open reading frame) is well understood in the art, as are the terms ORF 6 and ORF 6/7 with respect to adenovirus. The Examiner's attention is directed to Halbert et al. (1985, J. Virol. 56:250-257; a copy of this reference is attached hereto as Exhibit A), which describes ORF 6/7 in Figure 2 on page 251. ORF 6/7 refers to a region comprising the N-terminus of ORF 6 and the C-terminus of ORF 7. This reference clearly establishes that the term "ORF 6/7" was well understood by one of ordinary skill in the art at the time this invention was made.

Applicants respectfully submit that, in view of the foregoing remarks and Exhibit A attached hereto, the Examiner's rejection of claim 33 is overcome, should be withdrawn, and claim 33 is in condition for allowance.

The Examiner contends that the phrase "consisting essentially thereof (sic, of)" is vague and indefinite as used in claims 34 and 35.

Applicants respectfully submit that the term "consisting essentially of" is a ubiquitous phrase in patent claims having a clear meaning under pertinent case law. See Faber, *Landis on Mechanics of Patent Claim Drafting, Third Edition*, § 8, Practising Law Institute: New York, 1990. Consequently, Applicants are retaining the phrase but amending the claims to recite that the E2 or E4 gene or portion thereof, respectively, is the only viral gene contained in the vector. The vector also contains the adenovirus ITR sequences and the encapsidation sequence. Thus, the claims as amended are directed to the same patentable subject matter as rejected claims 34 and 35, but avoid language the Examiner deems consistent with a composition of various components as opposed to a single macromolecular structure (the vector).

In view of the foregoing amendments and remarks, Applicants submit that the Examiner's rejection is obviated in part and overcome in part, should be withdrawn, and that claims 34 and 35 are in condition for allowance.

Applicants respectfully submit that in view of the foregoing amendments and remarks, all of the grounds for the Examiner's rejection under 35 U.S.C. § 112, first paragraph are obviated and the rejection should be withdrawn.

Discussion of the Section 102 Rejection

Claims 34 and 35 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Berkner or Bajocchi.

Applicants submit that the amended claims 34 and 35 are clearly directed to adenoviral vectors having as the sole adenoviral gene either the E2 gene or part thereof (claim 34), or the E4 gene or part thereof (claim 35). As discussed in detail below, neither Berkner nor Bajocchi suggests, much less teaches, such vectors.

Berkner is a review of the state of development of adenoviral vectors for the expression of heterologous genes. Berkner discloses that nonconditional helper-independent viruses can be generated by insertions in E3 or other nonessential regions, and that conditional helper-independent viruses can be generated by insertions in E1 or E4. These are first generation adenoviral vectors, which have the many disadvantages disclosed in the specification at page 2, lines 12-27. Berkner also discloses defective adenoviral vectors in which the gene of interest is joined to the SV40 T antigen, and the virus is passaged in CV-1 cells.

Berkner does not teach how to make or use the recombinant adenoviral vectors of claims 34 and 35. Berkner certainly fails to describe an adenoviral vector having either the E2 gene, or part thereof, or the E4 gene, or part thereof, as the sole viral gene. At most, Berkner provides wishful thinking and an invitation to experiment. Berkner speculates (at page 620) that *potential deletions* in E4 *may* permit larger gene inserts. Berkner suggests (at page 621) that all that is required in *cis* are the ITRs and a packaging sequence, and that this approach has the *potential* for enabling large substitutions. Berkner comments however (at page 617), that while plasmids containing the ITRs could *theoretically* be used to generate recombinants with large inserts "(t)his approach however, has not yet been developed." Berkner's speculations and wishful thinking would clearly not have suggested to one of ordinary skill in the

art that Applicants' claimed invention should be carried out and would have a reasonable likelihood of success.

The Examiner states that Bajocchi discloses a vector derived from a type 5 adenovirus that contains all of the E2 and E4 genes. Office Action, page 4. Bajocchi states, in relevant part: "The recombinant adenoviral (Ad) vectors used are based on the Ad type 5 (ref. 28), in which the left end of E1 and a portion of the E3 regions are deleted...." (Berkner, page 232, second column). Applicants agree that such a vector must have the E2 and E4 genes. Claim 34 is directed to a vector that contains the E2 gene or part thereof as the sole adenoviral gene. Claim 35 is directed to a vector that contains the E4 gene or part thereof as the sole adenoviral gene. Bajocchi can in no way anticipate the claimed invention of claims 34 and 35, because neither vector of claims 34 and 35 has both E2 and E4 genes, as taught by Bajocchi.

In view of the foregoing amendments and remarks, Applicants submit that neither Berkner nor Bajocchi suggests, much less teaches, the claimed invention. Accordingly, the Examiner's rejection is obviated and should be withdrawn.

Conclusion

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant application. In the event that a telephone interview would be helpful in advancing the prosecution of this application, Applicants' agent invites the Examiner to contact the undersigned or Mr. Martin Savitzky at the number shown below.

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Respectfully submitted,



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APPENDIX
U.S. Patent Application Serial No. 08/397,225
"DEFECTIVE ADENOVIRUS VECTORS AND
USE THEREOF IN GENE THERAPY"
RPR File No. EX93015G1-US
Claims Under Consideration

1. (Thrice Amended) A defective recombinant adenovirus comprising
ITR sequences,
an encapsulation sequence, and
a heterologous DNA sequence,
wherein an E1 gene has been rendered non-functional by deletion, and
wherein an E2 or E4 gene has been rendered non-functional by deletion.
2. (Twice Amended) An adenovirus according to claim 1, wherein
adenovirus sequences are from a canine adenovirus.
3. (Thrice Amended) An adenovirus according to claim 1, wherein
adenovirus sequences are from a human group C adenovirus.
6. (Thrice Amended) An adenovirus according to claim 1, wherein late
genes L1-L5 have been rendered non-functional by deletion.
9. (Twice Amended) An adenovirus according to claim 1, wherein an
E3 gene has been rendered non-functional by deletion.
10. (Twice Amended) An adenovirus according to claim 9, wherein an
L5 gene has been rendered non-functional by deletion.
11. (Twice Amended) An adenovirus according to claim 1, further
comprising a functional E3 gene under the control of a heterologous promoter.
12. (Thrice Amended) An adenovirus according to claim 1, wherein the
heterologous DNA sequence is selected from the group consisting of
therapeutic genes and genes encoding antigenic peptides.
13. (Thrice Amended) An adenovirus according to claim 12, wherein
the heterologous DNA is a therapeutic gene which encodes a product selected
from the group consisting of enzymes, blood proteins, hormones, lymphokines,
growth factors, neurotrophic factors, apolipoproteins, dystrophin,
minidystrophin, tumor suppresser genes, and coagulation factors.

14. (Twice Amended) An adenovirus according to claim 1, wherein the heterologous DNA encodes an antisense sequence.

15. (Twice Amended) An adenovirus according to claim 12, wherein the heterologous DNA encodes an antigenic peptide capable of generating an immune response against microorganisms, tumors, or viruses.

16. (Twice Amended) An adenovirus according to claim 15, wherein the gene encodes an antigenic peptide specific for a virus selected from the group consisting of the Epstein Barr virus, the HIV virus, the hepatitis B virus, and the pseudo-rabies virus.

17. (Twice Amended) An adenovirus according to claim 12, wherein the heterologous DNA sequence further comprises a promoter.

18. (Twice Amended) An adenovirus according to claim 12, wherein the heterologous DNA sequence further comprises a signal sequence.

19. (Twice Amended) A cell line comprising, integrated into its genome, the genes necessary to complement a defective recombinant adenovirus according to claim 1, wherein one of the complementing genes is under the control of an inducible promoter.

20. (Thrice Amended) A cell line according to claim 19, wherein it comprises, in its genome, an E1 gene and an E2 gene wherein the E2 gene is under the control of an inducible promoter.

21. (Twice Amended) A cell line according to claim 20, wherein it additionally comprises the E4 gene from an adenovirus.

22. (Thrice Amended) A cell line according to claim 19, wherein it comprises, in its genome, an E1 gene and an E4 gene wherein the E4 gene is under the control of an inducible promoter.

23. (Twice Amended) A cell line according to claim 19, further comprising a glucocorticoid receptor gene.

24. (Thrice Amended) A cell line according to claim 19, wherein it comprises E2 and E4 genes and the E2 and E4 genes are under the control of an inducible promoter.

25. (Twice Amended) A cell line according to claim 19, wherein the inducible promoter is an LTR promoter of MMTV.

26. (Thrice Amended) A cell line according to claim 19, wherein it comprises a gene encoding the 72 K protein of E2.

27. (Twice Amended) A cell line according to claim 19, wherein it is obtained from the line 293.

28. (Twice Amended) A composition comprising a defective recombinant adenovirus according to claim 1 and a pharmaceutically acceptable vehicle.

29. (Twice Amended) A composition comprising a recombinant adenovirus according to claim 10 and a pharmaceutically acceptable vehicle.

30. (Twice Amended) A composition according to claim 28 wherein the vehicle is pharmaceutically acceptable for an injectable formulation.

31. (Twice Amended) A defective recombinant adenovirus comprising
ITR sequences,
an encapsulation sequence, and
a heterologous DNA sequence,
wherein E3 and E4 genes have been rendered non-functional by deletion.

32. (Amended) An adenovirus according to claim 31, wherein late genes L1-L5 have been rendered non-functional by deletion.

33. (Amended) A cell line according to claim 19, comprising open reading frames ORF6 and ORF6/7 of E4.

34. (Twice Amended) A defective recombinant adenovirus consisting essentially of

ITR sequences,
an encapsulation sequence,
a heterologous DNA sequence, and
all or part of an E2 gene,
wherein the E2 gene or part thereof is the sole adenoviral gene.

35. (Twice Amended) A defective recombinant adenovirus consisting essentially of

[the] ITR sequences,
an encapsulation sequence,
a heterologous DNA sequence, and
all or part of an E4 gene,
wherein the E4 gene or part thereof is the sole adenoviral gene.